

ENVIRONMENTAL ASSESSMENT
FOR
BAMBERMYCINS (GAINPRO®) IN SUPPLEMENTAL FEED FOR CATTLE CONSUMING PASTURE

1. Date: October 2001

2. Name of applicant:

Sponsor:

Intervet Inc.
405 State Street
Millsboro, DE 19966

Agent:

Intervet Inc.
405 State Street
Millsboro, DE 19966

In the United States, Intervet Inc will be the distributor of the product and will control the premix manufacture.

3. Address:

Intervet Inc
405 State Street
Millsboro, DE 19966

4. Description of the proposed action:

Purpose of the action. A new animal drug application has been approved to expand the use of bambermycins in cattle consuming pasture from 10-20 mg/head/day to 10-40 mg/head/day. GAINPRO® (bambermycins) is marketed as a premix (Type A Medicated Article) which is incorporated in at least one pound and not more than ten pounds of supplemental cattle feed (Type C Medicated Feed) and is fed daily at a rate of 10 to 40 mg per head per day or the premix can be added to a Free-choice mineral supplement and consumed at a rate of 10-40 mg/head/day for increased rate of weight gain.

Populations. The number of cattle consuming pasture is projected to be 18 million per year. Of that number, 5.4 million are projected to be fed supplements daily. An estimation that 20% of the cattle consuming pasture would receive bambermycins is proposed. Therefore, the number of cattle consuming pasture that would receive bambermycins is projected to be one million.

The use of GAINPRO®, in feeds will be limited to feed manufacturers who use the new drug in feeds which they manufacturer for cattle consuming pasture (steers and heifers).

The use of the animal drug will be limited to use in supplemental feeds for cattle consuming pasture (steers and heifers) under the approval of this new drug application. The feeds will not contain any other drug substances. Feeds containing bambermycins will be fed daily to cattle (steers and heifers) consuming pasture. GAINPRO® will be used as a partial replacement for existing agents intended for the same purpose. It is the industry practice to incorporate a growth promotant agent in feeds fed to cattle consuming pasture. GAINPRO® will provide an alternative means for increasing rate of weight gain.

Mode of Administration: Oral (mixed into supplemental cattle feeds).

5. Identification of chemical substances that are the subject of the proposed action:

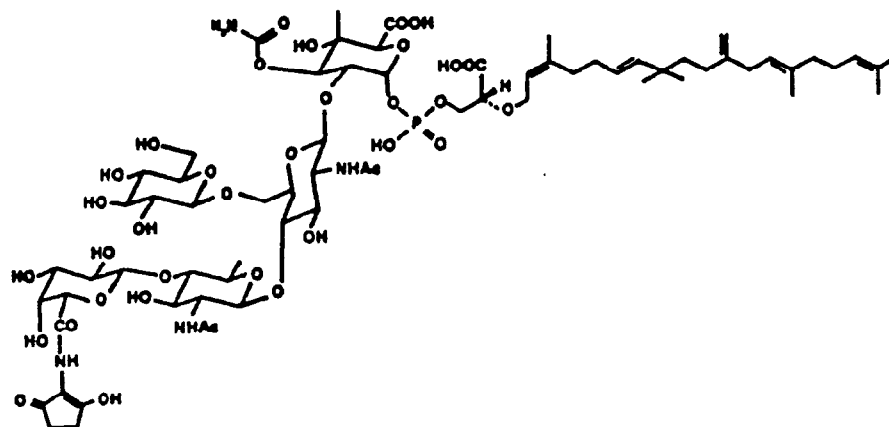
CHEMICAL/PHYSICAL PROPERTIES

The new drug is known as GAINPRO® (bambermycins) Growth Promotant Antibiotic -Type A Medicated Article.

Generic Name: Bambermycins

Chemical Abstract Service Registry No. 11015-37-5.

Bambermycins is a phosphorus-containing glycolipid which is obtained in the form of a colorless amorphous powder. The complete structure of this compound has not been elucidated. The major structural formula of bambermycins is:



Molecular Weight: 1700.

Molecular Formula: $C_{69}H_{107}N_4O_{35}P$

(C,48.5%; H,7.3%; O,37.3T; N,5.1%; P,1.8%)

Solubility: Bambermycins is soluble in water but not polar organic solvents.

Solvent	Solubility at 25°C (g/100 ml)
Water	25
Methanol	6.4
Ethanol	0.05
Acetone	0.01
Chloroform	0.01
Benzene	0.01

PRODUCT DESCRIPTION

Bambermycins is sold as GAINPRO® premix which is incorporated into supplemental feed of cattle consuming pasture. Bambermycins is the active ingredient in the GAINPRO® premix and is produced in a dried mycelial biomass form by a fermentation process. The GAINPRO® premix is sold in one concentration: 10 g bambermycins/lb of premix. In addition to the dried mycelial biomass the GAINPRO® premix may also contain diluents such as rice hulls, calcium carbonate, soybean oil and mineral oil.

ORIGIN OF BAMBERMYCINS

Bambermycins is formed by a group of grey-green streptomyces registered with the American Type Culture Collection (ATCC), comprising *Streptomyces bambergiensis* (ATCC 13879), *Strep. ghanaensis* (ATCC 14762), *Strep. geysiriensis* (ATCC 15503), and *Strep. ederensis* (ATCC 15304) and variants and mutants. Bambermycins is produced by fermentation. The entire mycelium is dried and used in the production of the feed additive GAINPRO®.

COMPOSITION OF THE MYCELIUM

Analysis of several mycelia batches containing bambermycins yielded the following average values (on a dry matter basis): Dry matter: 96.5%

Crude protein	33.1%	Lysine	0.58%
Crude ash	13.8%	Histidine	0.38%
Crude fiber	0.97%	Arginine	1.41%
Crude fat	3.97%	Aspartic acid	2.51%
Phosphorus	0.61%	Threonine	1.15%
Sodium	1.47%	Serine	1.07%
Potassium	1.26%	Glutamic acid	3.55%
Calcium	2.99%	Proline	0.88%
Arsenic	0.00002%	Glycine	1.77%
Lead	0.0015%	Alanine	2.33%
Chromium	0.0003%	Valine	1.48%
Iron	0.033%	Methionine	1.89%
Cobalt	0.0002%	Isoleucine	0.81%
Copper	0.0017%	Leucine	1.62%
Manganese	0.0032%	Tyrosine	0.89%
Mercury	0.00001%	Phenylalanine	0.89%
Zinc	0.0079%	Cystine	0.41%

MICROBIOLOGICAL SPECTRUM

Bambermycins *in vitro* is predominantly effective against gram-positive pathogenic bacteria; in streptococci, inhibitory values in the range of 0.001 mcg/ml can be shown; and at .05 mcg/ml in staphylococci. Bambermycins is less effective against gram-negative pathogenic microorganisms with the exception of *pasteurella* and *brucella*.

MODE OF ACTION

The beneficial effects (increased weight gain) of an antibiotic such as bambermycins are mediated through their effects on bacteria. In gram-positive bacteria, studies have shown that cell wall precursors accumulate in the presence of bambermycins; therefore, the mode of action against bacteria is inhibition of the synthesis of the bacterial cell wall.

The inhibiting effect of bambermycins against certain gram-negative bacteria that carry R factor has been shown by Watanabe¹ and others^{2,3,4} to be related to the presence of sex pili. The presence of sex pili causes these bacterial to be sensitive to bambermycins when they would not otherwise be sensitive^{1,2,5}.

6. Introduction of substances into the environment:

This Environmental Assessment (EA) is supplemental to the complete EA filed in the original NADA 44-759 (bambermycins for feedlot cattle). Reference is made to the original EA in NADA 44-759 (58 FR 54286, October 21, 1993) regarding introduction of substances from the manufacturing site and introduction of substances from the premix blending location.

Introduction of Substances from the Feed Mixing Locations.

Virtually all feed mixing would be done by feedmill companies that use GAINPRO® premix. The feed mixing locations must comply with current Good Manufacturing Practices for medicated feeds. With the required manufacturing controls for feed, inventory accountability and quality assurance procedures, the potential for release of bambermycins into the environment at these locations would be negligible.(58 FR 54286, October 21, 1993).

Introduction of Substances from the Use Site.

Bambermycins can be found in cattle manure and may be introduced into the soil at the use site. Because bambermycins is a naturally occurring antibiotic, it is rapidly degraded in soil and manure. In the original NADA 44-759 for feedlot cattle (58 FR 54286 October 21, 1993), degradation in four soil types, one of which contained cattle manure, demonstrated that bambermycins degraded with time. From bioassay analysis, the half-life of bambermycins ranged from 13.3 to 28.0 days for the four soil types. By day 55 of the study, degradation of bambermycins ranged from 72.0 to 98.5 percent for the four soil types.

Therefore, environmental exposure at the use site would be negligible from manure from cattle consuming bambermycins because of random dispersion on the land and because of rapid degradation in the soil.

Estimated amounts of Bambermycins Entering the Environment

Bambermycins is essentially not metabolized in the gastrointestinal tract and is excreted as the intact antibiotic in the cattle feces. This calculation assumes a worst case scenario in which one (1) acre of land is populated by 10 head of cattle. These 10 head are fed bambermycins for 150 days at a rate of 40 mg per head per day. It is assumed that the daily excreta from the animals will be a total of 10 kg of waste per animal. Thus, each 10 kg of waste will contain 40 mg bambermycins (4.0 ppm).

Concentration in water run-off from pasture:

During the feeding period there will be 2 inches of rainfall. Two inches of rainfall weighs 205,500 kg/acre. The total amount of bambermycins excreted in 150 days by 10 animals equals:

$$10 \text{ animals} \times 40 \text{ mg/animal} \times 150 \text{ days} = 60 \text{ grams}$$

Bambermycins is soluble in water; therefore it is assumed that all of the residue will be in the run-off. The maximum concentration of bambermycins in the run-off assuming no degradation equals:

$$60 \text{ grams}/205,500 \text{ kg of water} = 0.30 \text{ mg/kg (0.30 ppm)}$$

Concentration in soil from animal waste.

Assume no degradation of bambermycins. Assume random dispersion of manure from 10 animals per acre of land. Assume that the total amount of bambermycins excreted in 150 days by 10 animals on one acre of land equals 60 grams. Assume the manure will be incorporated into the top 3 inches of soil (weight of top 3" of soil in one acre equals 454,500 kgs).

The amount of bambermycins in the top 3 inches of soil per acre of land would equal:
 $60 \text{ grams}/454,500 \text{ kg} = 0.132 \text{ mg/kg (132 ppb)}$

As indicated by the above calculations, the amount of bambermycins (assuming no degradation) that would be released into the water and soil is extremely small. Based on the soil degradation and preliminary manure degradation studies in the original NADA 44-759, bambermycins is degraded rapidly. Therefore, the actual amounts of bambermycins that would get into the water or soil would be 3 to 10 times less than the estimated amounts.

Toxic substances.

There is no pollution of the environment in the manufacture, processing, and use of the new animal drug with heavy metal, pesticides, or radiation (58 FR 54286, October 21, 1993).

7. Fate of emitted substances in the environment:

The primary manner in which bambermycins would be introduced into the environment is through cattle manure randomly dispersed on the land. Any active bambermycins released into the environment is rapidly degraded. No other biologically active or hazardous components are contained in the dried mycelial biomass. The rate at which bambermycins undergoes degradation was investigated in four different soils (see Original NADA 44-759). The bambermycins concentration was monitored on days 0, 6, 13, 20, 27, 33, 41, 48, and 55 using a bioassay procedure. By day 55 of the study, degradation of bambermycins ranged from 72.0 to 98.5 percent for the four soil types. Therefore, the fate of bambermycins in cattle manure and in the soil is that of rapid loss of bioactivity.

8. Environmental effects of released substances:

Given the information developed in Items 6 and 7 above, it can be predicted that there will be no negative effects on animals, plants, humans, other organisms, and no effects at the ecosystem-level because of the rapid degradation of bambermycins in soil and soil containing cattle manure.

9. Use of resources and energy:

Reference is made to the original EA in NADA 44-759 (58 FR 54286, October 21, 1993) regarding the use of resource and energy. Manufacturing GAINPRO® premix will require an amount of energy similar to that used to produce and package any conventional fermentation product. The disposal of waste wash water and materials from the manufacturing process will not require the use of unusual amounts of natural resources.

10. Mitigation measures:

The use of GAINPRO® premix for cattle consuming pasture will not have any adverse effects on human health or the environment. No mitigation measures are necessary for GAINPRO® premix.

There are no known significant adverse environmental effects related to the manufacture and use of the new animal drug. The drug has been produced for use in cattle, poultry and swine in over 25 countries, and over nearly 33 years without reported adverse environmental effects.

11. Alternatives to the proposed action:

The only alternative to approval of the New Animal Drug Application is non-approval. This would mean that the cattle industry would not have the choice of use of this drug in cattle consuming pasture.

This drug will have the effect of providing an alternative means for increasing rate of weight gain in cattle consuming pasture.

No objections have been raised by an agency, organization, or individual. The drug has a history of safe manufacture and use in many countries including the United States. It has been authorized by the government of Germany for manufacture, and has been authorized for use in European Economic Community countries since 1968. Bambermycins has been used without incident for broiler chickens, turkeys and swine in the United States since 1975.

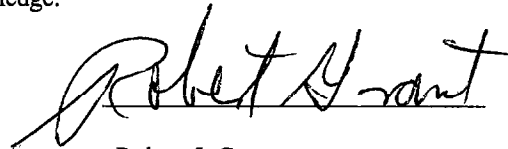
It is the sponsor's position that this action will not require the preparation of an environmental impact statement. It is the sponsor's belief that there is no significant risk associated with the proposed action. We have demonstrated in the application the usefulness of bambermycins in increasing rate of weight gain in cattle consuming pasture (steers and heifers). The significant benefits of approval of this NADA far outweigh the potential risks. This new animal drug application contains analytical methods for bambermycins in tissues and soil. It is concluded that the use of GAINPRO® premix for pasture cattle will not have any adverse effect on human health or the environment. Therefore, alternatives to the proposed action do not need to be considered.

12. List of preparers:

Robert J. Grant, Ph.D.
Senior Project Leader, Pharmaceuticals
Intervet Inc.

13. Certification

The undersigned petitioner certifies the information furnished in this Environmental Impact Analysis Report to be true, accurate and complete to the best of his knowledge.

DATE: 10/18/01

Robert J. Grant
Senior Project Leader, Pharmaceuticals

14.

References:

¹Host cell changes induced by R. factors and other sex factors. T. Watanabe, Y. Ogata, K. Sugawara, K. Oda, T. Saito, Y. Yokoyama. 6th Miles Internat'l Symposium on Molecular Biology (June 1972).

²Die Wirkung von Flavomycin auf episomal resistente Keime. G. Lebek, Abl. Vet. Med. 19: 532 (1972).

³The effect of Actinomycin D and Flavomycin on *E. coli* R+ strains. H. Brana, J. Hubacek and J. Konig. Folia Microbiol 18: 257-262 (1973).

⁴Inhibitory effect of Flavomycin as a feed additive on R factors in *E. coli* strains isolated from pig weanlings. A. Sokol, V. Kremery, F. Federic, V. Rajtar, J. Janouskova. Eighth international Congress of Chemotherapy (1973).

⁵ Additional antibiotic inhibitors of peptidoglycan synthesis. P.E. Linnet, J. L. Strominger, Antimicrob. Agents Chemotherapy 4 (3): 231-236 (1973).